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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,649	10/15/2001	John E. Ford	28110/37665	7526

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,649	FORD ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 29 October 2003 has been entered in full. Claims 13-14 are amended and claims 15 and 18 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 13-14 and 16-17 are pending and are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2-4 of the previous Office Action (30 July 2003) are *withdrawn in part* in view of the amended abstract and specification (29 October 2003). Please see section on Specification, below.

2. The rejection of claims 13-18 under 35 U.S.C. § 112, second paragraph at pg 9 of the previous Office Action (30 July 2003) is *withdrawn* in view of the amended and cancelled claims (29 October 2003).

Specification

3. The disclosure is objected to because of the following informalities:

3a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. The basis for this objection is set forth at pg 2-3 of the previous Office Action (30 July 2003). It is noted to Applicant that this objection will be maintained until the status of 09/687,860 changes or the instant application is deemed allowable.

Claim Rejections - 35 USC § 112

4. Claims 13-14, and 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a cancerous colon cell expressing the polypeptide of SEQ ID NO: 24 or a fragment that comprises at least amino acids 412-426 of SEQ ID NO: 24 in a biological sample, comprising (a) contacting the sample with an antibody or fragment thereof that specifically binds to the polypeptide of SEQ ID NO: 24 or a fragment that comprises at least amino acids 412-426 of SEQ ID NO: 24 for a time period sufficient to form a complex; and (b) detecting the complex, so that if a complex is detected it indicates the presence of the cancerous colon cell, and wherein the biological sample is a tissue or cell, does not reasonably provide enablement for a method of detecting a cancerous cell selected from the group consisting of a brain cancer, prostate cancer, breast cancer, skin cancer, lymphoma, sarcoma, colon cancer, leukemia, ovarian cancer, and pancreatic cell cancer, expressing an EGFL6 polypeptide in a biological sample, comprising (a) contacting the sample with an antibody or antigen binding fragment thereof that specifically binds to the polypeptide of SEQ ID NO: 24 or a fragment thereof for a time period sufficient to form a complex; and (b) detecting the complex, so that if a complex is detected it indicates the presence of the cancerous cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for claims 13-18 at pg 4-9 of the previous Office Action (30 July 2003).

The claims also recite that the EGFL6 polypeptide is selected from the group consisting of SEQ ID NO: 24, the amino acids 22 to 553 of SEQ ID NO: 24, and amino acids 412-426 of

SEQ ID NO: 24. The claims recite that the antibody is conjugated to a radioisotope, affinity label, enzymatic label, or fluorescent label. The claims recite that the biological is selected from the group consisting of tissue, cell, blood, serum, lymphatic fluid, urine, and cerebrospinal fluid.

Applicant's arguments (Paper No. 14, 20 November 2001), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts the Examiner's rejection (in that the specification does not teach any methods or working examples that detect all cancerous cells expressing the polypeptide of SEQ ID NO: 24 or all possible fragments of SEQ ID NO: 24) is mooted by the amendment of claim 13.

Applicant's arguments have been fully considered but are not found to be persuasive. Although claim 13 has been amended to specifically recite the type of cancer cells detected in the assay, the claims recite that the cells express any EGFL6 polypeptide. The specification of the instant application discloses that the polypeptide of SEQ ID NO: 6 or 24 (known as EGFL6) includes variants, isoforms, and fragments of at least 5 amino acids (pg 7, line 29; pg 8; pg 40-41). Therefore, the Examiner has interpreted claims 13 and 16-17 to encompass all possible fragments and variants of SEQ ID NO: 24. One skilled in the art cannot predict that all fragments and variants of EGFL6 are exclusive to SEQ ID NO: 24. Non-specific polypeptide fragments of SEQ ID NO: 24 may overlap with the amino acid sequences of other proteins. Therefore, the skilled artisan would be not be able to determine if the polypeptide fragment-antibody complex detected in the claimed method truly indicates that cells are expressing the

EGFL6 polypeptide of SEQ ID NO: 24. Furthermore, the non-specific fragment-antibody expression pattern may not be unique to only cancer cells.

(ii) Applicant contends that it would not require undue experimentation to examine the relationship between mRNA and protein expression for the claimed cancer types. Applicant argues that routine immunohistochemical analysis the EGFL6 antibody and the specific cancer tissues is well within the ability of one of skill in the art. Applicant indicates that routine experimentation to verify a claim is permitted should not be held against Applicant's insight to use the claimed antibodies as a cancer diagnostic. Applicant states that a continuation-in-part (U.S. Patent Application No. US 2003/0036508; pg 42-47; Tables 3-4) has been filed describing the results of experiments to give further support to the claims. Applicant indicates that EGFL6 polypeptide was detected using immunohistochemical on various types of normal and tumor tissues with an anti-EGFL6 primary polyclonal antibody. Applicant argues that ERHyl protein was differentially expressed in tumor tissue when compared to benign tissue in all tumor tissue types tested (U.S. Patent Application No. US 2003/0036508; pg 42-43).

Applicant's arguments have been fully considered but are not found to be persuasive. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present

invention is unpredictable and complex wherein one skilled in the art may not necessarily detect a cancerous cell expressing an EGFL6 polypeptide in a biological sample. Although the claimed method utilizes routine antibody binding techniques, the results of the method are unpredictable and complex when combined with the step of detecting a cancerous cell expressing *any* EGFL6 polypeptide in all possible biological samples.

The specification does not teach any methods or working examples that detect all possible fragments of SEQ ID NO: 24 in cells present in all possible types of biological samples. The specification does not teach detection of EGFL6 *protein expression* in any cancers, other than colorectal cancer tissue. Although the specification teaches that EGFL6 mRNA transcript is expressed in prostate cancer, breast cancer, colon cancer, lymphoma, sarcoma, and brain cancer (pg 114-117), the state of the art is such that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript (Haynes et al., Electrophoresis 19:1862-1872, 1998). One skilled in the art cannot predict that the EGFL6 mRNA transcript levels determined in various cancerous tissues are indicative of EGFL6 polypeptide (SEQ ID NO: 24) expression in cancerous cells. Applicant also indicates that EGFL6 polypeptide was detected in samples in U.S. Patent Application No. US 2003/0036508 using immunohistochemical on various types of normal and tumor tissues with an anti-EGFL6 primary polyclonal antibody. However, the instant specification and the specification of U.S. Patent Application No. US 2003/0036508 do not disclose any *specific* resulting numbers or percentages or statistical differences in EGFL6 protein staining for cell types other than colon cancer cells. Without this knowledge, which could not be gleaned from the instant specification or the specification of U.S. Patent Application No. US 2003/0036508, one of ordinary skill in the art at

the time the invention was made would not have been able to use the information obtained from these assays in a useful manner. Therefore, undue experimentation is required by the skilled artisan to detect EGFL6 polypeptide expression in all tumor tissues/cells, other than colon cancer.

Additionally, as discussed in the previous Office Action (30 July 2003), a large quantity of experimentation would be required of the skilled artisan to detect cancerous cells in any sample other than a cell or tissue. In Examples 6 and 8-9 of the specification, the *in situ* hybridization and protein expression studies are performed directly with normal and cancerous tissues. There are no methods or working examples in the specification to indicate that the EGFL6 polypeptide of SEQ ID NO: 24 is present in blood, serum, lymphatic fluid, urine, or cerebrospinal fluid. Undue experimentation would be required of one skilled in the art to develop and carry out studies examining EGFL6 polypeptide expression in various body fluids other than cells or tissue.

(iii) Applicant asserts that the specification contains adequate written description to enable a skilled artisan to detect the claimed EGFL6 polypeptide in biological samples. Applicant contends that immunoassay formats and means to modify said formats for specific antibodies were well known in the art at the time of filing. Applicant submits that one of skill in the art would understand how to identify the presence or absence of the EGFL6 polypeptide of the invention in any of the claimed biological samples using antibodies that recognize the EGFL6 polypeptide or immunogenic fragment thereof. Applicant states that based on the disclosure of the methods along with the level of skill and knowledge in the art, one of skill in the art would

recognize that the application was in possession of all the various methods necessary to practice the claimed invention.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, according to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". The specification outlines a prophetic procedure for detecting a cancerous cell expressing any EGFL6 polypeptide in all possible biological samples. However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily detect a cancerous cell expressing any EGFL6 polypeptide in all possible biological samples. As mentioned above, the present invention is unpredictable and complex wherein one skilled in the art may not necessarily detect a cancerous cell expressing an EGFL6 polypeptide in a biological sample. Although the claimed method utilizes routine antibody binding techniques, the results of the method are unpredictable and complex when combined with the step of detecting a cancerous cell expressing *any* EGFL6 polypeptide in all possible biological samples. Furthermore, the instant specification and the specification of U.S. Patent Application No. US 2003/0036508 do not disclose any *specific* resulting numbers, percentages or statistical differences for the level of EGFL6 protein staining in cells other than colon cancer cells. Without this knowledge, one of ordinary skill in the art at the time the invention was made would not have been able to use the information obtained from these assays in a useful manner.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to detect EGFL6 protein expression in all

possible cancers other than colon cancer, to detect a cancerous cell expressing the polypeptide of SEQ ID NO: 24 in all possible biological samples other than cells and tissue, and to generate and detect the infinite number of fragments and variants of SEQ ID NO: 24, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of correlating mRNA transcript levels to protein expression, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

5. Claims 13-14 and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 13-14 and 16-17, the acronym "EGFL6" renders the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

7. Claims 13-14 and 16-17 recite the limitation "the polypeptide of SEQ ID NO: 24 or a fragment thereof" in claim 13, line 6. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
23 February 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER